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(12) **Patent:** (11) **CA 929483**

(54) PROCESS FOR PREPARING SUBSTITUTED PHENYLALKANOIC ACIDS

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ABSTRACT:

CLAIMS: Show all claims

*** Note: Data on abstracts and claims is shown in the official language in which it was submitted.

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PROCESS FOR PREPARING SUBSTITUTED PHENYLALKANOIC ACIDS

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This invention relates to a process for preparing L-α-hydrazino-β-phenylpropionic acids.

More particularly, this invention relates to a process for preparing L-α-hydrazino-β-phenylpropionic acids by photolytically decomposing an azidoformamido acid.

It is known in the art that various α-hydrazino-β-phenylpropionic acids are useful as decarboxylase inhibitors. It is further known that the D-isomer of these acids is generally inactive and may even be antagonistic to the action of the L-form, thereby reducing its potency.

In the past, it has been the accepted practice to separate stereoisomers by the formation of diastereomeric salts with either optically active bases or acids, depending on the nature of the racemate. However, with the hydrazino compounds of the present invention, separation is complicated by the fact that some diastereomeric salts do not form crystalline materials with sufficiently different properties so that the diastereomers can be readily crystallized. In some instances, the diastereomeric salts are oily or waxy materials which become difficult if not impossible to separate by conventional means. Quite obviously, if a relatively simple and inexpensive process could be found which would preferentially produce the desired L-α-hydrazino-β-phenylpropionic acids, it would receive widespread acceptance in the art.

Accordingly, it is an object of this invention to provide a process for preparing L-α-hydrazino-β-phenylpropionic acids. Other objects will become apparent from the ensuing description of this invention.

These objects are accomplished by the present invention which provides a process for preparing the L-form of a compound of the formula:

wherein:

R, R_1 and R_2 each may be hydrogen or loweralkyl;

which comprises photolytically decomposing the L-form of a compound of the formula:

wherein:

R, R_1 and R_2 are as previously defined.

As used above the "loweralkyl" radical signifies an alkyl group containing from 1 to about 6 carbon atoms which can be straight chained or branched.

In order to obtain the starting materials for the above photolysis reaction the corresponding L-α-amino-β-phenyl-propionic acid is reacted with phosgene and sodium azide.

The photolysis reaction of this invention preferably takes place in the presence of water and may be carried out at a temperature of from about -50°C. to about +100°C., preferably -20°C. to +20°C.

The following examples are presented to further illustrate the invention.

EXAMPLE 1

L-α-hydrazino-α-methyl-β-(3,4-dihydroxyphenyl)propionic acid

L-α-methyl-3,4-dihydroxyphenylalanine sesquihydrate (119.1 g., 0.5 mole) and toluene are placed in a flask and refluxed. By means of a Dean-Stark* separator water is azeotroped away and toluene is returned to the flask. When the theoretical amount of water is distilled the mixture is concentrated to dryness in vacuo. The residue is taken up in 500 ml. of methanol and the mixture saturated at 0-5°C. with gaseous hydrogen chloride. The mixture is allowed to stand at 0°C. for 42 hours and is then concentrated to dryness to yield L-α-methyl-3,4-dihydroxyphenylalanine methyl ester.

To the ester (67.58 g., 0.3 mole) from the previous step slurried with tetrahydrofuran (1 l.) at 55-70°C. is passed phosgene at the rate of 0.5 mole per hour. After two hours nitrogen is bubbled through the mixture as it is allowed to cool to room temperature. The solution is concentrated in vacuo to obtain L-α-chlorocarbonyl-α-methyl-β-(3,4-carbonyldioxyphenyl)alanine methyl ester.

The ester of the previous step is taken up in dimethoxyethane (500 ml.), powdered sodium azide (19.5 g., 0.3 mole) is added and with stirring the mixture is refluxed for 3 hours. The mixture is filtered, the filtrate concentrated in vacuo to dryness and the residue crystallized from acetone-hexane to yield L-α-N-azidocarbonyl-α-methyl-β-(3,4-carbonyldioxyphenyl)alanine methyl ester.

The ester (32.03 g., 0.1 mole) so obtained is stirred overnight at 25°C. with 1 N hydrochloric acid (100 ml.). The mixture is concentrated in vacuo to dryness to yield L-α-N-azidocarbonyl-α-methyl-β-(3,4-dihydroxyphenyl)-

*t.m.

alanine. To the residue is added 300 ml. of water and the mixture warmed to 80°C. with stirring then cooled to 0°C. The mixture is photolysed at 0°C. with a low pressure mercury arc. The mixture is diluted to 1 l. with water, warmed to 90°C., filtered and the filtrate cooled to room temperature. The cooled filtrate was absorbed on Amberlite-IR-120® on the acid ($H_3O^{\oplus}$) cycle. Elution with 1 N ammonium hydroxide and concentration of the eluate to dryness in vacuo yields crude product. On recrystallization L-α-hydrazino-α-methyl-β-(3,4-dihydroxyphenyl)propionic acid is obtained.

EXAMPLE 2

L-α-hydrazino-β-(3,4-dihydroxyphenyl)propionic acid

L-3,4-dihydroxyphenylalanine (98.6 g., 0.5 mole) is taken up in 500 ml. of methanol and the mixture saturated at 0-5°C. with gaseous hydrogen chloride. The mixture is allowed to stand at 0°C. for 42 hours and is then concentrated to dryness to yield L-3,4-dihydroxyphenylalanine methyl ester.

To the ester (63.37 g., 0.3 mole) from the previous step slurried with tetrahydrofuran (1 l.) at 55-70°C. is passed phosgene at the rate of 0.5 mole per hour. After two hours nitrogen is bubbled through the mixture as it is allowed to cool to room temperature. The solution is concentrated in vacuo to obtain L-α-chlorocarbonyl-β-(3,4-carbonyldioxyphenyl)alanine methyl ester.

The ester of the previous step is taken up in dimethoxyethane (500 ml.), powdered sodium azide (19.5 g., 0.3 mole) is added and with stirring the mixture is refluxed for 3 hours. The mixture is filtered, the filtrate concentrated in vacuo to dryness and the residue crystallized from acetone-hexane to yield L-α-N-azidocarbonyl-β-(3,4-carbonyldioxyphenyl)alanine methyl ester.

The ester (30.62 g., 0.1 mole) so obtained is stirred overnight at 25°C. with 1 N hydrochloric acid (100 ml.). The mixture is concentrated in vacuo to dryness to yield L-α-N-azidocarbonyl-β-(3,4-dihydroxyphenyl)alanine. To the residue is added 300 ml. of water and the mixture warmed to 80°C. with stirring then cooled to 0°C. The mixture is photolysed at 0°C. with a low pressure mercury arc. The mixture is diluted to 1 l. with water, warmed to 90°C., filtered and the filtrate cooled to room temperature. The cooled filtrate was absorbed on Amberlite-IR-120® on the acid ($H_3O^{\oplus}$) cycle. Elution with 1 N ammonium hydroxide and concentration of the eluate to dryness in vacuo yields crude product. On recrystallization L-α-hydrazino-β-(3,4-dihydroxyphenyl)propionic acid is obtained.

EXAMPLE 3

L-α-ethyl-α-hydrazino-β-(3,4-dihydroxyphenyl)propionic acid

L-α-ethyl-3,4-dihydroxyphenylalanine (112.6 g., 0.5 mole) is taken up in 500 ml. of methanol and the mixture saturated at 0-5°C. with gaseous hydrogen chloride. The mixture is allowed to stand at 0°C. for 42 hours and is then concentrated to dryness to yield L-α-ethyl-3,4-dihydroxyphenylalanine methyl ester.

To the ester (71.8 g., 0.3 mole) from the previous step slurried with tetrahydrofuran (1 l.) at 55-70°C. is passed phosgene at the rate of 0.5 mole per hour. After two hours nitrogen is bubbled through the mixture as it is allowed to cool to room temperature. The solution is concentrated in vacuo to obtain L-α-chlorocarbonyl-α-ethyl-β-(3,4-carbonyldioxyphenyl)alanine methyl ester.

The ester of the previous step is taken up in dimethoxyethane (500 ml.), powdered sodium azide (19.5 g., 0.3 mole) is added and with stirring the mixture is refluxed for 3 hours. The mixture is filtered, the filtrate concentrated in vacuo to dryness and the residue crystallized from acetone-hexane to yield L-α-N-azidocarbonyl-α-ethyl-β-(3,4-carbonyldioxyphenyl)alanine methyl ester.

The ester (33.43 g., 0.1 mole) so obtained is stirred overnight at 25°C. with 1 N hydrochloric acid (100 ml.). The mixture is concentrated in vacuo to dryness to yield L-α-N-azidocarbonyl-α-ethyl-β-(3,4-dihydroxyphenyl)-alanine. To the residue is added 300 ml. of water and the mixture warmed to 80°C. with stirring then cooled to 0°C. The mixture is photolysed at 0°C. with a low pressure mercury arc. The mixture is diluted to 1 l. with water, warmed to 90°C., filtered and the filtrate cooled to room temperature. The cooled filtrate was absorbed on Amberlite-IR-120® on the acid ($H_3O^{\oplus}$) cycle. Elution with 1 N ammonium hydroxide and concentration of the eluate to dryness in vacuo yields crude product. On recrystallization L-α-ethyl-α-hydrazino-β-(3,4-dihydroxyphenyl)propionic acid is obtained.

EXAMPLE 4

L-α-hydrazino-α,β-dimethyl-β-(3,4-dihydroxyphenyl)propionic acid

L-α,β-dimethyl-3,4-dihydroxyphenylalanine (112.6 g., 0.5 mole) is taken up in 500 ml. of methanol and the mixture saturated at 0-5°C. with gaseous hydrogen chloride. The mixture is allowed to stand at 0°C. for 42 hours and is then concentrated to dryness to yield L-α,β-dimethyl-3,4-dihydroxyphenylalanine methyl ester.

To the ester (71.8 g., 0.3 mole) from the previous step slurried with tetrahydrofuran (1 l.) at 55-70°C. is passed phosgene at the rate of 0.5 mole per hour. After two hours nitrogen is bubbled through the mixture as it is allowed to cool to room temperature. The solution is concentrated in vacuo to obtain L-α-chlorocarbonyl-α,β-dimethyl-β-(3,4-carbonyldioxyphenyl)alanine methyl ester.

The ester of the previous step in taken up in dimethoxyethane (500 ml.), powdered sodium azide (19.5 g., 0.3 mole) is added and with stirring the mixture is refluxed for 3 hours. The mixture is filtered, the filtrate concentrated in vacuo to dryness and the residue crystallized from acetone-hexane to yield L-α-N-azidocarbonyl-α,β-dimethyl-β-(3,4-carbonyldioxyphenyl)alanine methyl ester.

The ester (33.43 g., 0.1 mole) so obtained is stirred overnight at 25°C. with 1 N hydrochloric acid (100 ml.). The mixture is concentrated in vacuo to dryness to yield L-α-N-azidocarbonyl-α,β-dimethyl-β-(3,4-dihydroxyphenyl)-alanine. To the residue is added 300 ml. of water and the mixture warmed to 80°C. with stirring then cooled to 0°C. The mixture is photolysed at 0°C. with a low pressure mercury arc. The mixture is diluted to 1 l. with water, warmed to 90°C., filtered and the filtrate cooled to room temperature. The cooled filtrate was absorbed on Amberlite-IR-120® on the acid ($H_3O^{\oplus}$) cycle. Elution with 1 N ammonium hydroxide and concentration of the eluate to dryness in vacuo yields crude product. On recrystallization L-α-hydrazino-α,β-dimethyl-β-(3,4-dihydroxyphenyl)propionic acid is obtained.

EXAMPLE 5

L-α-hydrazino-α,β,β-trimethyl-β-(3,4-dihydroxyphenyl) propionic acid

L-α,β,β-trimethyl-3,4-dihydroxyphenylalanine (119.6 g., 0.5 mole) is taken up in 500 ml. of methanol and the mixture saturated at 0-5°C. with gaseous hydrogen chloride. The mixture is allowed to stand at 0°C. for 42 hours and is then concentrated to dryness to yield L-α,β,β-trimethyl-3,4-dihydroxyphenylalanine methyl ester.

To the ester (75.99 g., 0.3 mole) from the previous step slurried with tetrahydrofuran (1 l.) at 55-70°C. is passed phosgene at the rate of 0.5 mole per hour. After two hours nitrogen is bubbled through the mixture as it is allowed to cool to room temperature. The solution is concentrated in vacuo to obtain L-α-chlorocarbonyl-α,β,β,-trimethyl-(3,4-carbonyldioxyphenyl) alanine methyl ester.

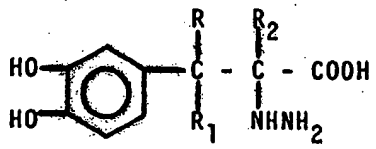
The ester of the previous step is taken up in dimethoxyethane (500 ml.), powdered sodium azide (19.5 g., 0.3 mole) is added and with stirring the mixture is refluxed for 3 hours. The mixture is filtered, the filtrate concentrated in vacuo to dryness and the residue crystallized from acetone-hexane to yield L-α-N-azidocarbonyl-α,β,β-trimethyl-β-(3,4-carbonyldioxyphenyl) alanine methyl ester.

The ester (34.83 g., 0.1 mole) so obtained is stirred overnight at 25°C. with 1 N hydrochloric acid (100 ml.). The mixture is concentrated in vacuo to dryness to yield L-α-N-azidocarbonyl-α,β,β-trimethyl-β-(3,4-dihydroxyphenyl) alanine. To the residue is added 300 ml. of water and the mixture warmed to 80°C. with stirring then cooled to 0°C. The mixture is photolysed at 0°C. with a low pressure

mercury arc. The mixture is diluted to 1 l. with water, warmed to 90°C., filtered and the filtrate cooled to room temperature. The cooled filtrate was absorbed on Amberlite-IR-120® on the acid ($H_3O^{\oplus}$) cycle. Elution with 1 N ammonium hydroxide and concentration of the eluate to dryness in vacuo yields crude product. On recrystallization L-α-hydrazino-α,β,β-trimethyl-β-(3,4-dihydroxyphenyl)propionic acid is obtained.

The embodiments of the invention in which an exclusive property or privilege is claimed are defined as follows:

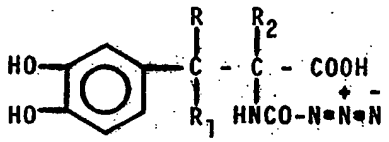
1. A process for preparing the L-form of a compound of the formula:



wherein:

R, R_1 and R_2 each may be hydrogen or loweralkyl;

which comprises photolytically decomposing the L-form of a compound of the formula:



wherein:

R, R_1 and R_2 are as previously defined.

2. The process of Claim 1 wherein the photolysis reaction is carried out in the presence of water.

3. The process of Claim 2 wherein the photolysis reaction is carried out at a temperature of from about $-20^{o}C.$ to about $+20^{o}C.$

4. The process of Claim 1 wherein R and R_1 are hydrogen and R_2 is methyl.

5. The process of Claim 1 wherein R, R_1 and R_2 are all hydrogen.

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ABSTRACT OF THE DISCLOSURE

Process for converting L-α-amino-β-phenyl propionic acids to L-α-hydrazino-β-phenylpropionic acids by photolytically decomposing an azidocarbonyl group in the presence of water at a temperature range of from -50°C. to about +100°C.

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